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09/179,002	10/26/1998	VIDYA BRAJ LOHRAY	DRF 3.0-019.	5185

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EXAMINER	
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ART UNIT	PAPER NUMBER
1624	
MAIL DATE	DELIVERY MODE
11/02/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	09/179,002	LOHRAY ET AL.	
	Examiner	Art Unit	
	/Venkataraman Balasubramanian/	1624	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *23 August 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *See Continuation Sheet* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) *1-3,5-9,24-27,29-31,33,34,65-68,71,72,74,75,77,79,80,82,83 and 85-99* is/are allowed.

6)☒ Claim(s) *10,70 and 100-111* is/are rejected.

7)☒ Claim(s) *78* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Continuation of Disposition of Claims: Claims pending in the application are 1-3,5-10,24-27,29-31,33,34,65-68,70-72,74,75,77,79,80,82,83 and 85-111.

DETAILED ACTION

Applicants' response filed on 8/23/2007, is made of record.

Claims 1-3, 5-10, 24-27, 29-31, 33, 34, 65-68, 70-72, 74, 75, 77-80, 82, 83 and 85-111 are now pending. In view of applicants response the following claim objection and rejections are applied.

Claim Objections

Claim 78 is objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. Claim 78 recites solvate, which is not in the scope of claim 77 on which it is dependent

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 10 and 70 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The following apply. Any claim not specifically rejected is rejected as it dependent on a rejected claim and shares the same indefiniteness.

1. Claim 10 is indefinite for more than one reason. Claim 10, as recited, is product by process claim. It is dependent on claims 6-9 respectively and there is no showing that the compound made by any one of these claims is different frm

each other. A product is a product irrespective of how it is made. The processes attributes are independent limitation and do not necessarily define the structural make-up of the product. A claim is not rendered patentably distinct by a process directed to its preparation even though the process may be patentable. Note "Determination of patentability in "product by process" claims is based on product itself, even though such claims are limited and defined by process, and thus product in such claim is unpatentable if it is same as, or obvious from, product of prior art, even if prior product was made by different process" In re Thorpe 227 USPQ 964. Also note In re Brown, 459 F.2d 531, 535, 173 USPQ 685, 688 (CCPA 1972), the court held that "The lack of physical description in a product by process claim makes determination of the patentability of the claim more difficult, since in spite of the fact that the claim may recite only process limitations, it is the patentability of the product claimed and not of the recited process steps which must be established."

In the instant case, the compounds embraced in the claim 10 would be the same compound irrespective how these compounds are made. Specification has no showing that a process of making the compound would alter the structural make-up of the final product although the final product is same.

2. Claim 70 is indefinite as it recites "treatment of prophylaxis...". Deletion of "of prophylaxis" is suggested as it would be consistent with deletion of prophylaxis in related claim 29.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any

person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 100-111 are rejected under U.S.C. 112, first paragraph, because the specification while being enabling for treating diabetes, does not reasonably provide enablement for treating or preventing any or all diseases or any or all cancers generically embraced in these claims. The specification does not enable any physician skilled in the art of medicine, to use the invention commensurate in scope with these claims.

The instant method of use claims 100-111 are drawn to preventing and treating large list of diseases including any or all caner based on the mode of action of instant compounds as HMG CoA reductase inhibitors, PPARa, PPARg agonists etc. in general.

Instant claims, as recited, are reach through claims. A reach through claim is a claim drawn to a mechanistic, receptor binding or enzymatic functionality in general format and thereby reach through a scope of invention for which they lack adequate written description and enabling disclosure in the specification.

In the instant case, based on the inhibition of HMG CoA reductase and or as PPARa and PPARg agonism by the instant compounds, instant claims reaches through inhibiting and treating any or all diseases in general and thereby they lack adequate written description and enabling disclosure in the specification.

More specifically, in the instant case, based on the mode of action of instant compounds as inhibition of HMG CoA reductase and or as agonist of PPARa and PPARg, based on limited assay, it is claimed that preventing and treating

any or all diseases including any or all cancers in general, which there is no enabling disclosure.

The scope of the claims includes preventing or treating hyperlipemia, hypercholesteremia, hyperglycemia, osteoporosis, obesity, glucose intolerance, leptin resistance, insulin resistance, or diseases in which insulin resistance is the underlying pathophysiological mechanism, type 11 diabetes, impaired glucose tolerance, dyslipidaemia, disorders related to Syndrome X such as hypertension, obesity, atherosclerosis, hyperlipidemia, coronary artery disease and other cardiovascular disorders, certain renal diseases including glomerulonephritis, glomerulosclerosis, nephrotic syndrome, hypertensive nephrosclerosis, retinopathy, nephropathy, disorders related to endothelial cell activation, psoriasis, polycystic ovarian syndrome (PCOS), improving cognitive functions in dementia, diabetic complications, osteoporosis, inflammatory bowel diseases, myotonic dystrophy, pancreatitis, arteriosclerosis, xanthoma or cancer for which there is no enabling disclosure. In addition, the scope of these claims includes preventing and treating various cancers, which would include including lung cancer, bone cancer, pancreatic cancer, skin cancer. cancer of the head or neck, cutaneous or intraocular melanoma, uterine cancer, ovarian cancer, rectal cancer, cancer of the anal region. stomach cancer, colon cancer, breast cancer, uterine cancer, carcinoma of the fallopian tubes, carcinoma of the endometrium, carcinoma of the cervix, carcinoma of the vagina, carcinoma of the vulva, Hodgkin's disease, cancer of the esophagus, cancer of the small intestine, cancer of the endocrine system, cancer of the thyroid gland, cancer of the

parathyroid gland, cancer of the adrenal gland, sarcoma of soft tissue, cancer of the urethra, cancer of the penis, prostate cancer, chronic or acute leukemia, lymphocytic lymphomas, cancer of the bladder, cancer of the kidney or ureter, renal cell carcinoma, carcinoma of the renal pelvis, neoplasms of the central nervous system (CNS), primary CNS lymphoma, spinal axis tumors, brain stem glioma, pituitary adenoma, or a combination of one or more of the foregoing cancers, which is not adequately enabled solely based on the activity of the compounds provided in the specification. The instant compounds are disclosed to have HMG CoA reductase inhibitory activity and have agonist of PPARa and PPARg and it is recited that the instant compounds are therefore useful in treating any or all diseases stated above for which applicants provide no competent evidence. It appears that the applicants are asserting that the embraced compounds because of their mode action as HMG CoA reductase inhibitor and or agonist of PPAR that would be useful for all sorts of diseases and cancers. However, the applicants have not provided any competent evidence that the instantly disclosed tests are highly predictive for all the uses disclosed and embraced by the claim language for the intended host. Moreover many if not most of diseases such as psoriasis, lung cancer, brain cancer, pancreatic cancer, colon cancer etc. are very difficult to treat and despite the fact that there are many anticancer drugs.

The scope of the claims involves millions of compounds of claim 1 as well as the thousand of diseases embraced by the term cancer and other diseases.

Proliferative disease would include benign tumors, malignant tumors, polyps, lumps, lesions, other pre-cancerous conditions, psoriasis, leukemia, the hyper proliferation of the gastric epithelium caused by the Helicobacter pylori infection of ulcers.

Cancer is just an umbrella term. Tumors vary from those so benign that they are never treated to those so virulent that all present therapy is useless.

No compound has ever been found to treat proliferative diseases of all types generally. Since this assertion is contrary to what is known in medicine, proof must be provided that this revolutionary assertion has merits. The existence of such a "compound" is contrary to our present understanding of oncology. Cecil Textbook of Medicine states, "each specific type has unique biologic and clinical features that must be appreciated for proper diagnosis, treatment and study" (see the enclosed article, page 1004). Different types of cancers affect different organs and have different methods of growth and harm to the body. Thus, it is beyond the skill of oncologists today to get an agent to be effective against cancers generally.

The term " prophylaxis" actually means to prevent spread of a disease (as per Meriam Webster's Dictionary). "To prevent" actually means to anticipate or counter in advance, to keep from happening etc. (as per Websters II Dictionary) and therefore it is not understood how one skilled in the art can reasonably establish the basis and the type of subject to which the instant compounds can be administered in order to have the "prevention" effect. Further, there is no evidence on record which demonstrates that the in-vitro screening test relied

upon is recognized in the art as being reasonably predictive of success in any of the contemplated areas of 'prevention'.

Note substantiation of utility and its scope is required when utility is "speculative", "sufficiently unusual" or not provided. See Ex parte Jovanovics, 211 USPQ 907, 909; In re Langer 183 USPQ 288. Also note Hoffman v. Klaus 9 USPQ 2d 1657 and Ex parte Powers 220 USPQ 925 regarding type of testing needed to support in vivo uses.

Next, applicant's attention is drawn to the Revised Utility and Written Description Guidelines, at 66 FR 1092-1099, 2001 wherein it is emphasized that 'a claimed invention must have a specific and substantial utility'. The disclosure in the instant case is not sufficient to enable the instantly claimed method treating solely based on the inhibitory activity disclosed for the compounds. The state of the art at the time of instant invention is indicative of the requirement for undue experimentation. See Khan et al., Diabetes Care 25(4), 708-771, 2002 and Iida et al., FEBS Letters 520, 177-181, 2002.

In evaluating the enablement question, several factors are to be considered. Note *In re Wands*, 8 USPQ2d 1400 and *Ex parte Forman*, 230 USPQ 546. The factors include: 1) The nature of the invention, 2) the state of the prior art, 3) the predictability or lack thereof in the art, 4) the amount of direction or guidance present, 5) the presence or absence of working examples, 6) the breadth of the claims, and 7) the quantity of experimentation needed.

1) The nature of the invention: The method of use claims are drawn to besides treatment, prevention of any and all cancer and variety of diseases and

disorders. However, specification provides no support for preventing all or any disorders. In fact based on the specification and examples, it appears that the instant compounds are mainly PPAR and HMG CoA reductase inhibitors and may be useful for treating disorders of diabetes wherein these receptor are implicated. Specification has not provided any evidence or nexus that because of the mode of action of the instant compound, the compound would be useful for preventing and treating all or any said disorders and cancers. Such a reasonable correlation is necessary to demonstrate such utilities. See Ex parte Stevens, 16 USPQ 2d 1379 (BPAI 1990); Ex parte Busse et al., 1 USPQ 2d 1908 (BPAI 1986) (the evidence must be accepted as "showing" such utility, and not "warranting further study"). The evidence presented in this case does not show such utilities related to 'prevention', but only warrants further study.

2) The state of the prior art: Recent publications expressed that the inhibition effects of HMG CoA reductase and agonists of PPAR are unpredictable and are still exploratory and agonists See Khan et al., and Iida et al., cited above.

3) The predictability or lack thereof in the art: Applicants have not provided any competent evidence or disclosed tests that are highly predictive for the pharmaceutical use for treating and preventing all the said diseases and any or all cancers by the instant compounds. Pharmacological activity in general is a very unpredictable area. Note that in cases involving physiological activity such as the instant case, "the scope of enablement obviously varies inversely with the degree of unpredictability of the factors involved". See *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970).

4) The amount of direction or guidance present and 5) the presence or absence of working examples: Specification has no working examples to show treating and or preventing any or all cancers or various diseases positively recited in the instant claims and the state of the art is that the effects of HMG CoA reductase inhibitors and agonists of PPAR are unpredictable.

6) The breadth of the claims: The instant claims embrace treating and preventing any or all cancers and various diseases with huge genus of compounds.

7) The quantity of experimentation needed would be an undue burden to one skilled in the pharmaceutical arts since there is inadequate guidance given to the skilled artisan, regarding the pharmaceutical use, for the reasons stated above.

Thus, factors such as "sufficient working examples", "the level of skill in the art" and "predictability", etc. have been demonstrated to be sufficiently lacking in the instant case for the instant method claims. In view of the breadth of the claims, the chemical nature of the invention, the unpredictability of enzyme-inhibitor interactions in general, and the lack of working examples regarding the activity of the claimed compounds towards treating the variety of diseases of the instant claims, one having ordinary skill in the art would have to undergo an undue amount of experimentation to use the instantly claimed invention commensurate in scope with the claims.

MPEP §2164.01(a) states, "A conclusion of lack of enablement means that, based on the evidence regarding each of the above factors, the specification, at the time the application was 'filed, would not have taught one skilled in the art how to make and/or use the full scope of the claimed invention

without undue experimentation. In re Wright, 999 F.2d 1557,1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993)." That conclusion is clearly justified here and undue experimentation will be required to practice Applicants' invention.

This rejection is same as made in the previous office action but now includes claims 100-111. Applicants' traversal is not persuasive.

First of all, as noted above, instant claims are reach through claims. Again, based on the mode of action, based on the limited assays (pages 90-96), applicants are asserting that any disease wherein PPAR is present can treated and can be prevented for which there is no evidence provided. Applicants rely on two articles but both of which clearly suggest further experimentation. In fact one the article is a protocol for clinical studies.

Secondly, applicants assert that diabetes can be prevented and any disease related Syndrome X can be prevented but have not offered any evidence showing such is the case. Currently there are several antidiabetic agents which show similar glucose lowering activity but they have not prevented diabetes.

Thirdly, applicants assert the said compounds can be used to prevent diabetes another diseases stated therein. Yet claims 31, 33, 34 and other incorporate additional active ingredients. If the instant compounds are able to prevent the said diseases why would one need additional active ingredients ?. Note MPEP 2164.08(b) which states that claims that read on "... significant numbers of inoperative embodiments would render claims nonenabled when the specification does not clearly identify the operative embodiments and undue

experimentation is involved in determining those that are operative.". Clearly that is the case here.

Hence, this rejection is proper and is maintained.

Allowable Subject Matter

Claims 1-3, 5-9, 24-27, 29-31,33, 34, 65-68, 71, 72, 74, 75, 77, 79, 80, 82-83 and 85-99 are allowed. It is noted that EP 0 903 343 cited on the Form PTO-892 discloses compounds within the present claims but has an publication date subsequent to the present filing date. Note, however, that any U.S. patent corresponding to the European patent would constitute prior art against the present claims and/or involve interfering subject matter.

Conclusion

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication from the examiner should be addressed to Venkataraman Balasubramanian (Bala) whose telephone number is (571) 272-0662. The examiner can normally be reached on Monday through Thursday from 8.00 AM to 6.00 PM. The Supervisory Patent Examiner (SPE) of the art unit 1624 is James O. Wilson, whose telephone number is 571-272-0661. The fax phone number for the organization where this application or proceeding is assigned (571) 273-8300. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (571) 272-1600.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAG. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-2 17-9197 (toll-free).

Venkataraman Balasubramanian

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10/29/2007